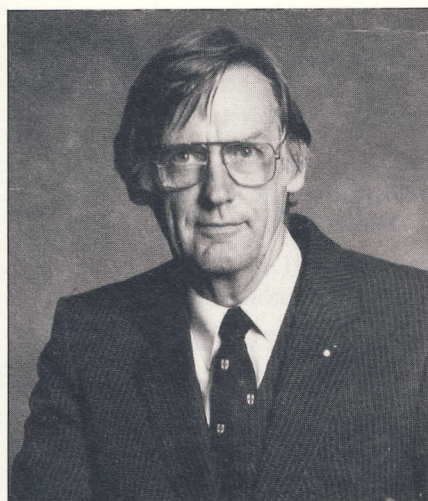


## Angina Pectoris – Part II: A general practice review of the treatment – EL Murray



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### Curriculum vitae

Elliot Murray was born in Durban in 1931. He obtained a degree in Civil Engineering from the University of Natal in 1954. He got married in 1953, moved to East London for a while before going to Cape Town where he qualified in medicine in 1961. After a house job at Edendale hospital he went into general practice in East London where he has remained. Elliot has been interested in post-graduate education for GPs and obtained the MFGP in 1976 and the MPraxMed, from Pretoria in 1977. At present he is a member of the Academy Council and Regional Director of Vocational Training in the East London/Ciskei area.

### Summary

*Part II deals with the treatment of both stable and unstable Angina, stressing the fact that unstable angina is serious and needs intensive care treatment. The three available calcium antagonists are evaluated, emphasizing the different ways in which they work.*

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### KEYWORDS:

Angina Pectoris; Drug Therapy; Physician, Family.

In the first part of this paper the aetiology and diagnosis of angina was discussed. The concept that stable and unstable angina pectoris are different diseases with different aetiologies and vastly different risk factors, was stressed.

In this second part the treatment of both stable and unstable angina is discussed, highlighting the fact that unstable angina is a very dangerous condition needing intensive care treatment with later assessment for possible revascularisation procedures.

The three very good calcium antagonists which are available to us at present, work in different ways and this difference must be appreciated.

The development of tolerance to long acting nitrates, is discussed.

Before discussing treatment it must be emphasised that Unstable and Stable Angina are two very different conditions.

Stable Angina can be treated in most

cases by the General Practitioner on an outpatient basis with admission to hospital being only rarely required. Unstable Angina on the other hand must always be treated in hospital, preferably in an Intensive Care Unit. With the exception of mild cases of angina of recent onset, which has a better prognosis, these cases are better treated by a Physician.

### TREATMENT OF STABLE ANGINA PECTORIS

There are four steps in the treatment, vis:

- i. Reassurance and explanation
- ii. Life style modification
- iii. Drug therapy
- iv. Revascularisation procedures

#### i. Reassurance and Explanation

##### a. Circadian rhythm:

The body's metabolism is slowest in the morning. The patient will suffer more angina in the early morning so that activity should be saved for later in the day. The majority of cardiac incidents occur in the first four hours after awakening.

##### b. The warm up phenomenon:

Apart from the Circadian rhythm, patients are able to perform more actively once the muscles have become warmed-up. Walking home from the shops is usually easier than the outward journey.

##### c. Sexual intercourse:

Explanation must be given to couples rather than only to the patient. There is less chance of getting angina if sex is performed more than two hours

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after a meal. Angina can be prevented by the prophylactic use of a beta blocker or sublingual nitrate. The exercise equivalent is that of climbing two flights of stairs or exercising to a heart rate of 120 beats per minute.

d. We must explain to the patient that angina is a warning of potential damage to the heart and defines the limits to exercise or stress.

### ii. Life Style Modification

#### a. Slowing down where appropriate:

Patient must have rest periods if necessary.

#### b. Appropriate exercise:

Why do we recommend exercise? Exercise has been shown to lower the heart rate and BP at rest and at submaximal work load and so improves functional capacity. Exercise modifies the lipids and increases the high density lipoprotein. Exercise consumes calories. There is a psychological benefit and the patients become more compliant with the reduction of risk factors.

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Activity should be left for later on in the day.

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How can this exercise be achieved and how much is recommended?

If one has the exercise stress testing facility available, this shows clearly how much exercise the patient can safely perform. If EST is not available the patient can be advised to perform low level exercise. The resting heart rate is noted and the patient exercises to within 20 beats of this figure. He

aims at walking one and a half kilometres in 15 to 20 minutes. If he gets angina while exercising, he must reduce the rate and not the duration of exercise.

#### c. Risk factor modification

Risk factors must be looked for and measured and where appropriate, modified. No patient may smoke and the patient and family unit must be told about the danger of passive smoking and avoid it.

### iii. Drug Therapy

#### A. Nitrates

The nitrates act by vasodilation which leads to peripheral pooling, decreased venous return and diminished ventricular volumes and pressure. This decreases the preload which in turn reduces the myocardial oxygen requirements. Nitrates also reduce arterial and arteriolar tone which lowers systemic pressure, left ventricular volume and afterload - also reducing the myocardial oxygen needs.

In the coronary circulation they relieve coronary spasm. The nitrates redistribute blood along collaterals and from epicardial to endocardial sites.

In animal experiments nitrates can cause vasodilation in the ischaemic zone. Nitrates are effective against vasospastic angina and angina at rest. Dynamic stenosis (coronary artery spasm) and organic spasm can occur at same site - both respond to nitrates and calcium antagonists.

#### Side Effects

Hypotension, headaches (which disappear after several days of

continued use, possibly due to tolerance) and nausea.

Available as:

#### Sublingual tablets

Glyceryl trinitrate (TNT)  
Isosorbide dinitrate (ISDN)

#### Oral tablets ISDN

Isosorbide mononitrate (ISMN)

Ointment TNT ISDN

Patches TNT

Intravenous infusion TNT

Lingual spray ISDN TNT

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Patients need to know that Angina is a warning.

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#### Tolerance

Single doses are effective, but with sustained treatment after one week effect may wear off considerably as measured by the drop in BP and time on treadmill to ischaemic changes. Patients must have a low nitrate period to maintain maximal effect.

Oral tablets should be taken at meal times only so that there is a long break in medication from supper to breakfast time. This low medication period reduces the tendency towards the development of tolerance.

If patches are used they should also be removed at bed time so as to have a low nitrate period.

Once one understands that patients may develop a tolerance to nitrates, it helps to distinguish between worsening angina needing an increase in the drug and a relative drug failure

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which needs alternative therapy or spacing of the nitrate therapy.

Tolerance does not develop to sublingual nitrates because of the short sharp rise in nitrate levels, with low nitrate periods between the tablets.

All patients must be supplied with sublingual nitrates which can either be TNT or ISDN, and they must be instructed in the use of the tablets, vis:

1. The tablets must be used sublingually or chewed for rapid action.
2. If headache is a problem, once the angina has settled the rest of the tablet can be spat out.
3. TNT tablets must be fresh and carried in a dark glass bottle without cotton wool or padding.
4. The tablets must be used prophylactically if a certain action (eg sexual intercourse) causes angina.
5. The tablets are cheap and effective and do not lose their effect if used in quantity and do not cause addiction.
6. Small quantities should be prescribed as once the seal is broken the tablets start deteriorating in only eight weeks. If stored in the refrigerator they can last up to six months.
7. The tablets take 1-2 minutes to work and the effect lasts for up to 30 minutes.
8. Patients should preferably be sitting and a tablet used every three minutes until pain goes or until four or five tablets have been used. If the pain persists the patient must contact his doctor.
9. Sublingual nitrates should cause a burning sensation locally and cause an increase in heart rate which should last for about ten minutes if tablets are still effective.

### *B. Beta Blocking Agents*

These agents have been the cornerstone in the therapy of angina pectoris and hypertension, but are now increasingly challenged by the calcium antagonists.

The adrenoceptors are classified as Alpha or Beta types. The Beta receptors are divided into Beta 1 and Beta 2.

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Most cardiac incidents occur during the first four hours after awakening.

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Beta 1 are found in heart muscle; Beta 2 are found in bronchial and vascular smooth muscle, but some are also in the myocardium.

Beta agonists stimulate production of AMP which in turn "opens" calcium channels to promote a positive inotropic effect (contraction). In the SA node pacemaker the current is increased (positive chronotropic effect).

The Beta blockers block appropriate receptor sites by a lock and key effect which obstructs the above mechanisms.

Beta blockers lower heart rate (HR) for any given work load and reduces the mean BP. The double product (HR x Syst BP) is a measure of myocardial oxygen demand.

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Beta blockade reduces HR and contractility and hence cardiac output. This results in a drop in BP.

All beta blockers are potentially equally effective in angina pectoris and choice of drug matters little. It is important to become familiar with one or two - possibly a short acting drug and a cardioselective longer acting beta blocker.

Twenty per cent of patients with angina do not respond to any beta blocker, possibly because of:

- i) The significant role played by coronary artery spasm.
- ii) The underlying severe obstructive coronary artery disease (CHD) which may be responsible for angina at a low level of exertion and at a heart rate of 100 or less.
- iii) An abnormal increase on LV end diastolic pressure because of excess negative inotropic effect and resultant decrease in subendocardial blood flow.

The aims of treatment should be to abolish anginal pain or secure a resting heart rate of 55-60 and exercise heart rate of less than 100. It may not be possible to achieve these low heart rates with drugs possessing intrinsic sympathomimetic activity (ISA).

The list of contraindications is very long, but the most important is asthma, or a past history of asthma, or peripheral vascular disease. Even cardioselective drugs can cause problems as this selectivity is relative.

Beta blockers can be freely combined with nitrates and nifedipine. They should only be combined with

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verapamil or diltiazem with caution as the combination may cause excessive bradycardia or atrioventricular block.

### *Impaired LV function*

In these patients beta blockers may improve angina at the cost of lessening exercise tolerance. One can use digoxin and diuretics, but it is probably better to avoid beta blockers in CCF.

### *Beta Blockade Withdrawal*

Sudden withdrawal may precipitate angina or even MI, unless the patient is at strict bed rest.

### *Possible Side Effects*

Depression, bad dreams, general malaise, weakness and the worsening of Raynaud's phenomenon or claudication.

### *C. Calcium Channel Antagonists*

Calcium is vital in the genesis of cardiac action potential, regulation of myocardial contractility and contraction of smooth muscle. Calcium channel blocking agents interfere with the entry of calcium into the cell (by blocking the slow channel) and so may reduce the formation and conduction of the cardiac impulse, reduce myocardial contractility and produce arterial vasodilatation. By this means, they reduce myocardial oxygen demand, increase myocardial oxygen supply and reduce blood pressure.

We have three very effective agents available to us, viz: Verapamil, Diltiazem and Nifedipine and each differ from one another in their chemical structure, their mechanism

of action at a cellular level and their pharmacological effect. This heterogeneity gives the group a distinct advantage over the beta blockers which are more homogenous in their action.

Nifedipine produces coronary and systemic vasodilatation, but in vivo has little effect on the cardiac conducting system. In contrast, both Verapamil and Diltiazem produce less vasodilatation than Nifedipine, but impair the action of the sinoatrial and atrioventricular node.

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If patient experiences Angina while exercising, reduce the *rate* and not the *duration* of exercise.

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### *Verapamil*

Be careful in myocardial depression due to beta blockers, Digoxin, Quinidine or Disopyramide (Rhythmolan or Norpace). Caution is also advised in Hypertrophic Obstructive Cardiomyopathy and renal impairment.

Adverse effects:  
Mainly constipation.

Drug interactions:  
Depression of AV node with Digoxin and/or beta blockers.

Dosage:  
80-120 mg. three times a day - doses must be individualised. With chronic therapy, twice daily dosage is adequate.

### *Diltiazem*

We must be wary of excessive

bradycardia, second or third degree heart block and with compromised ventricular function or a conduction defect.

Adverse effects:  
Constipation, ankle oedema, flushing.

Drug interactions:  
Combined with Digoxin and/or beta blockers may cause excessive bradycardia.

Dosage:  
30-60 mg three or four times daily, increasing to 90 mg three or four times daily. Long acting 90 mg tablets can be used twice daily.

### *Nifedipine*

The drug is very readily absorbed orally and rapidly sublingually. A capsule bitten and fluid allowed to remain in the mouth for a short while is useful in preventing angina. It does not, however, replace sublingual nitrates in getting rid of pain.

This drug is excreted by the kidneys.

Be careful in severe cardiac failure, aortic stenosis and hypertrophic obstructive cardiomyopathy.

Adverse effects:  
Peripheral vasodilation, flushing, dizziness. May produce peripheral oedema and may worsen angina initially. Muscle cramps might be a problem.

Watch for vasodilatory effects and hypotension.

Dosage:  
10 mg three or four times a day, building up to 20mg per dose. We have 5mg capsules for initial use in the elderly.

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Emotion related angina, as well as cold-induced pain, are suggestive of an increase in coronary resistance and will probably respond better to a calcium antagonist than to other antianginal drugs.

Implementation of Drug Therapy

All patients are prescribed and instructed in the use of sublingual nitrates.

All patients are given Aspirin, unless there is an Aspirin allergy. The dose has not been finally and definitely stated, but half or one Aspirin a day with a meal appears to be the optimum dose.

If the sublingual nitrate is adequate, the patient is observed and encouraged to lead a healthy life style.

If this treatment does not control symptoms adequately and if the patient has to use more than two sublingual tablets a week, the next

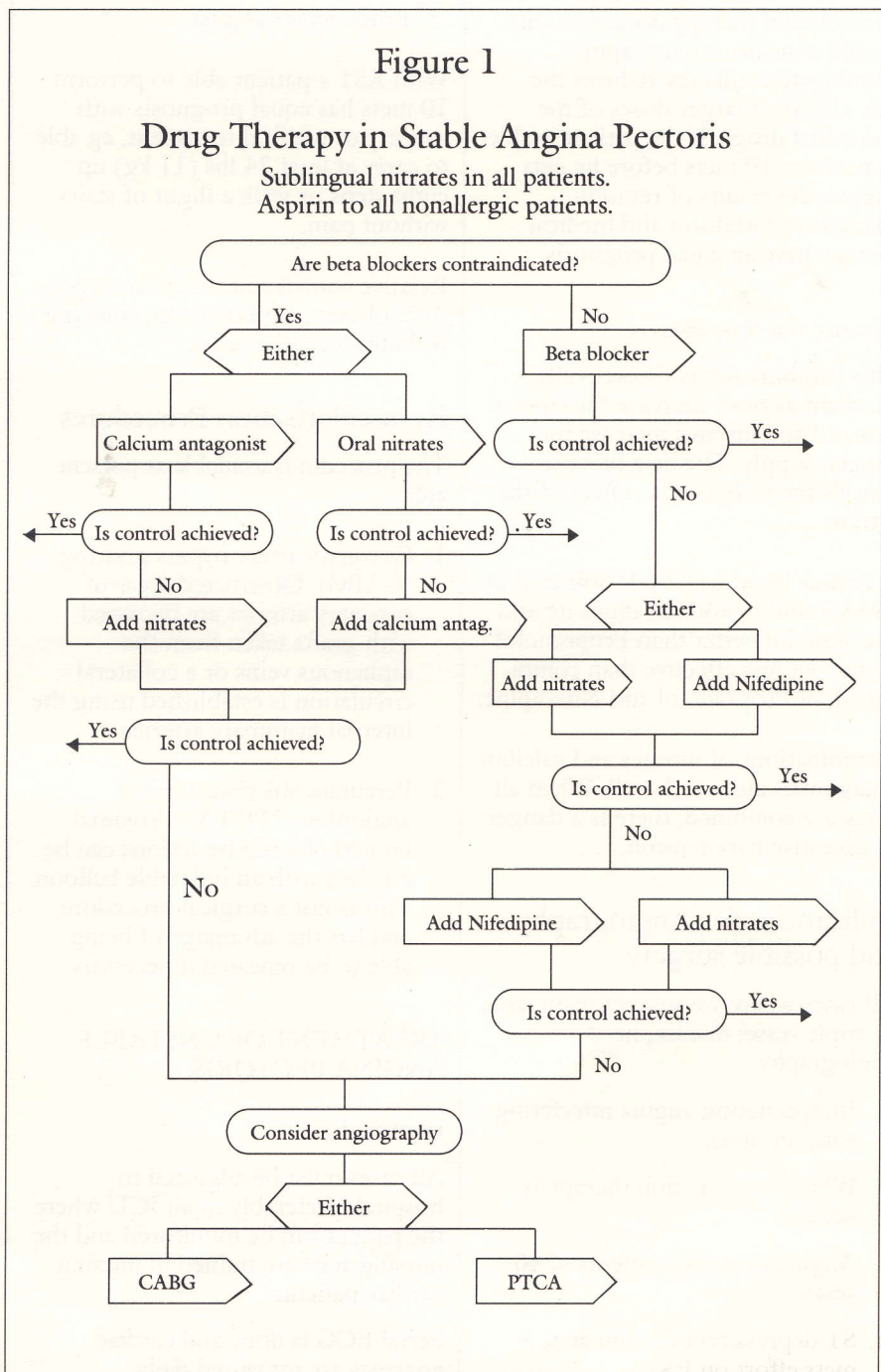
Patients do develop a tolerance to oral nitrates.

step is to decide on whether to initiate treatment with an oral nitrate, a beta blocker or a calcium antagonist.

If the patient has a contraindication to a beta blocker the choice is narrowed. The nitrates are the cheapest option, but the beta blockers offer cardio protection in reducing the chances of myocardial infarction and Nifedipine has been shown to reduce the formation of

new atherosclerotic lesions in the coronary arteries.

The flow sheet in Figure 1 is a suggested model.



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## Combination Therapy

Some authorities state that once combination therapy is needed, one should consider angiography. Combination therapy reduces the side effects of larger doses of the individual drugs. If the patient is able to perform 10 mets before he gets angina, the results of revascularisation procedures and medical therapy have an equal prognosis.

*Nitrates and Beta Blockers*

This combination is theoretically excellent as both decrease the oxygen demand and nitrates increase the oxygen supply. The beta blocker cancels the tachycardiac effect of the nitrate.

A double blind trial by Morse et al in 1985 found isosorbide dinitrate and Propranolol better than Propranolol alone, but less effective than combination of Propranolol and Nifedipine.

Combinations of nitrates and calcium antagonists also work well. When all three are combined, there is a danger of excessive hypotension.

## Indications for Angiography and possible surgery

All cases where we suspect main stem or triple vessel disease, need angiography:

- Incapacitating angina interfering with life style.
- Where combination therapy is needed.
- Angina in young patients < 40 years.
- ST depression of 2 mm at < 3 mets effort on EST.

- Unstable angina unless surgery is contraindicated.
- Prinzmetal's angina.

With EST a patient able to perform 10 mets has equal prognosis with surgery or medical treatment, eg able to carry at least 24 lbs (11 kg) up eight steps or walk a flight of stairs without pain.

Relative contraindications to surgery: Age, obesity, hypertension, smoking, diabetes, varicose veins.

## Revascularisation Procedures

The procedures available at present are:

- Coronary artery bypass grafting (CABG). Obstructed areas of coronary arteries are bypassed with grafts taken from the saphenous veins or a collateral circulation is established using the internal mammary arteries.
- Percutaneous transluminal angioplasty (PCTA). Proximal limited obstructive lesions can be crushed with an inflatable balloon. This is not a surgical procedure and has the advantage of being able to be repeated if necessary.

## TREATMENT OF UNSTABLE ANGINA PECTORIS

## General

All cases must be admitted to hospital, preferably to an ICU where the patient can be monitored and the nursing staff are trained in nursing cardiac patients.

Serial ECG is done and cardiac enzymes are measured daily.

The patient is sedated with Diazepam.

Morphine is used to achieve adequate pain relief.

All patients are given Oxygen therapy at 2-4 litres/minute.

IV line is established with 5% Dextrose water drip.

The patient is kept at strict bed rest, except for the use of a bedside commode.

## Specific Treatment

IV Heparin is given to increase the partial thromboplastin time (PTT) to two or three times normal for three to five days.

Sublingual nitrates are given as necessary.

If it is not contraindicated, use a beta blocker, eg Propranolol or a cardioselective drug to reduce the heart rate to about 60 (bearing in mind the intrinsic sympathomimetic activity (ISA) effect of some Beta Blockers). If no relief in eight hours, add Nifedipine to the beta blocker and if this does not provide relief of pain, nitrates can be used intravenously or by the transdermal route.

Once the patient is stabilised, he is given Aspirin one tablet daily and slowly mobilised. If the patient is not stabilised readily, he needs emergency angiography as the prognosis in cases with pain after 48 hours of bed rest is very poor with a one year survival rate of 57%.

If beta blockers are contraindicated, or if the patient is having angina at rest, or if the patient is already taking adequate doses of beta blockers, then a calcium antagonist, plus nitrates

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should be started at time of admission.

Combinations of drugs need very careful monitoring because of brady or tachycardias and the danger of hypotension. The prognosis in patients who have mild or moderate angina of recent onset is better than in patients with crescendo angina which are much better handled by a cardiologist.

Identifying those patients who will progress to an acute myocardial infarct is mainly a matter of the doctor's personal judgment and those who deal more often with these cases have this sense more finely tuned. An early unfavourable outcome was recently also linked to the occurrence of silent ischaemic episodes.

All cases of UAP must be followed up with at least an EST to try and determine those who need to have revascularisation procedures. This EST is done at about two months after stabilisation.

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